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UTILITY PATENT APPLICATION TRANSMITTAL

(only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	JBP 461
First Named Inventor or Application Identifier	John Kung
Express Mail Label No.	EJ474009100US

APPLICATION ELEMENTS

See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO:

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form *(attached hereto in duplicate)*
2. ☒ Specification [Total Pages 27]
(Preferred arrangement set forth below)
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R&D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure

3. ☐ Drawing(s)*(35 USC 113)* [Total Sheets]
4. Oath or Declaration
   a. ☐ Newly executed (original or copy)
   b. ☒ Unexecuted original
   c. ☐ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional check boxes 5 and 16)
      i. ☐ Deletion of Inventor(s)
      Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation by Reference
(useable if Box 4c is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4c, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
14. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. ☐ Other:

16. ☐ If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information:*
Amend the specification by inserting before the first line: -- This is a ☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.: , filed . --

17. For this divisional application, please cancel original Claims of the prior application before calculating the filing fee.

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SIGNATURE		
DATE	July 27, 1999	

COMPOSITIONS FOR STABILIZING OXYGEN-LABILE SPECIES

Reference to copending patent applications: This patent application is being filed simultaneously with U.S. Patent Application Serial No. ____ (Attorney Docket No. NEU-017; inventors Christopher Stahl and Frederick Woodin) and hereby incorporates herein the disclosure of such patent application by reference.

Field of the Invention

This invention relates to compositions and methods for stabilizing oxygen-labile species in compositions. More particularly, it relates to compositions containing one or more oil- and/or water-soluble oxygen-labile species and one or more stabilizing elements. It also relates to methods of making such compositions and methods of using such compositions.

Background of the Invention

For many years, it has proven difficult to make stable compositions containing oxygen-labile species. "Oxygen-labile" species are those that are easily oxidized and readily decompose when exposed to the environment. Such oxygen-labile species are, therefore, very difficult to formulate into compositions in combination with other compounds that may accelerate such decomposition or that may be exposed to the environment over time. In recent years, it has become desirable, for example, to include various vitamin compounds in topical skin care compositions in order to nourish or repair the skin. However, those of ordinary skill in the art have found that these vitamin compounds are quite unstable in topical compounds due to the fact that they are easily oxidized and decompose quickly, resulting in loss of efficacy and discoloration of the composition.

Thio compounds such as metabisulfite and sulfite compounds have been known as good water-soluble antioxidants and have been added to compositions to prevent such oxidation problems. However, these compounds may cause sensitization in certain individuals and are not useful for administration to humans. They also possess noxious odors and are unpleasant to use. Japanese Patent Publication No. 53-7488, for example,

suggests that combining ascorbic acid with dl-N-acetyl homocysteine thiolactone or N-acetyl-L-cysteine and sulfite in an aqueous solution of ascorbic acid results in a composition that can be stored stably over a long period.

EP 0 349 797 B1 mentions the combination of N-acetylcysteine and ascorbic acid or ascorbate as a stabilizer for the N-acetylcysteine. Slovakian publication, Farm. Obzor - LIV - 1985 p. 513 (Pharmacology Review) mentions the combination of N-acetylcysteine and ascorbic acid at a pH of 6.2. Both N-acetylcysteine and ascorbic acid are water-soluble. However, none of these references indicate that N-acetylcysteine would serve to stabilize an oil-soluble oxygen-labile species.

Thus, it is an object of this invention to provide compositions that contain oxygen-labile species that are stable over long periods of time.

It is another object of this invention to provide compositions that contain oil-soluble and/or water-soluble oxygen-labile species that are stable over long periods of time.

Yet another object of this invention is to provide compositions that contain both oil-soluble and water-soluble oxygen-labile species that are stable over long periods of time.

It is another object of this invention to provide methods of making stable compositions containing oxygen-labile species.

Another object of this invention is to provide methods of using the stable oxygen-labile species-containing compositions of this invention.

Yet another object of this invention is to provide skin care compositions that contain oxygen-labile species such as vitamins and their derivatives for topical use on the skin.

Summary of the Invention

We have discovered that certain oil-soluble and/or water-soluble oxygen-labile species may be stabilized in compositions by the addition of one or more stabilizer compounds. Such stabilizer compounds are selected from the following categories:

a) thio-containing compounds, such as sulfites and cysteine derivatives; and

b) glycoproteins, such as lactoferrin.

Oil-soluble oxygen-labile species may include vitamin compounds such as retinoids, choleciferol, vitamin K, tocotrienol and tocopherol derivatives, essential fatty acids and the like. Water-soluble oxygen-labile species may include vitamin compounds such as ascorbic acid and its derivatives, niacin, thiamine, riboflavin, folic acid, pyrodoxine, pantothenic acid, niacinamide, lipoic acid, dihydrolipoic acid, essential amino acids and the like. The oil-soluble oxygen-labile species may be present in the compositions of this invention in amounts of from about 0.01 to about 10%. The water-soluble oxygen-labile species may be present in the compositions of this invention in amounts of from about 0.01 to about 20%.

Detailed Description of the Preferred Embodiments

The compositions of this invention contain certain oil-soluble and/or water-soluble oxygen-labile species which are stabilized in compositions by the addition of one or more stabilizer compounds. Such stabilizer compounds are selected from the following categories:

a) thio-containing compounds, such as sulfites and cysteine derivatives; and

b) glycoproteins, such as lactoferrin.

The stabilizers which are included in the term "thio-containing compounds" include such compounds as sulfites and metabisulfites, cysteine derivatives and glutathione. More preferably, the thio-containing compounds are cysteine derivatives. Most preferably, the thio-containing compound is N-acetylcysteine. Thio-containing compounds are well-known as stabilizers of water-soluble compounds as they reside in the water phase of compositions. However, they are not known to be capable of stabilizing oil-soluble compounds as they do not reside in the oil phase of compositions. Surprisingly, we have found that compositions containing both water- and oil-soluble oxygen labile species as well as thio-containing compounds are stable over long periods of time. Preferably, the amount of thio-containing compound should range from about 0.001 to about 5% of the

weight of the composition. More preferably, there should be from about 0.01 to about 0.5% of the composition by weight.

Furthermore, compositions containing oil-soluble and/or water-soluble oxygen labile species and stabilizer compounds, selected from the group of glycoproteins are surprisingly stable. The glycoproteins that are useful in the compositions of this invention include lactoferrin and the like. Unexpectedly, such glycoproteins, large molecules that reside in the water phase of compositions, and which are known to be biologically active have proven to be viable as stabilizer compounds in the compositions of this invention. Although it is unknown how these proteins serve to stabilize the compositions of this invention, it is theorized that the proteins may reside at the oil/water interface of the compositions of this invention and are therefore active in both phases. Alternatively, the proteins may somehow adsorb or attract the ions that would otherwise cause oxidation of the oxygen-labile species of the compositions of this invention. Preferably, the amount of glycoprotein compound should range from about 0.00001 to about 5% of the weight of the composition. More preferably, there should be from about 0.01 to about 1% of the composition by weight.

Most preferably, the glycoprotein useful in the compositions of this invention is lactoferrin, a milk-derived protein that chelates iron and has a molecular weight of 80,000 daltons. Although lactoferrin is known as an anti-free radical compound in biological systems, it has heretofore been unknown for use in formulations. Whether an antioxidant or chelator which is active in a biological system will be active in a composition is completely unpredictable.

The oxygen-labile species may exist in the compositions of this invention either individually or as a combination. For example, vitamins A, C or E may be present in the compositions of this invention individually, i.e., one of such vitamins in one composition. Alternatively, various combinations of vitamins may be present within an individual composition, for example, vitamin C (ascorbic acid) may be present in a composition with either thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both. Vitamins A and C may be present within an

individual composition with thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both to achieve a stable formulation. Vitamins C and E may be present within an individual composition with thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both. Vitamins A, C and E may also be present in an individual composition with thio-containing compounds or a glycoprotein or both. Surprisingly, in each of these compositions, both the water-soluble and oil-soluble oxygen-labile species are stable over a long period of time. One of ordinary skill in the art would expect that vitamins A and C together would not be stable as Vitamin C tends to sacrifice itself to stabilize Vitamin A. Compositions of this invention containing both Vitamins A and E together, we have found, preferably contain at least about 0.0001% of Vitamin C for ensuring stability of all materials.

The compositions of this invention may be utilized in dosage forms suitable for cosmetic or pharmaceutical use. For example, the compositions of this invention may be made in the forms of emulsions, creams, lotions, gels, essences, milks, toners, hydroalcoholic solutions, multivesicular systems, suspensions, patches, masks, sticks, and other dosage forms suitable for therapeutic use, including oral administration forms.

The compositions of this invention may be made using conventional formulation technology. For example, in a standard oil-in-water emulsion, the starting water phase should be purged with either nitrogen or argon to displace any residual oxygen. Alternatively, the water phase may be heated to 80°C and held at that temperature at least about ten minutes to reduce oxygen solubility. A conventional oil phase should be made and the oil phase poured into the water phase. After phasing, the formulation should be blanketed with an inert gas such as nitrogen or argon and the formulation permitted to cool to room temperature. As the temperature reaches 45° C, the stabilizer compound should be added to the formulation. The stabilizer compound should be mixed into the formulation for about ten minutes, after which the oxygen-labile species may be introduced into the formulation. Neutralization to the appropriate pH may be made prior to or subsequent to the addition of the oxygen-labile species, depending upon the oxygen-

labile species utilized. For example, neutralization is preferred subsequent to adding ascorbic acid, but should be accomplished prior to adding retinol. The formulation resulting from this process should be packaged in an oxygen-impermeable package, such as an aluminum tube.

The pH of the formulations of this invention is preferably in a range that is suitable for a particular oxygen-labile species used in the compositions. The pH should reflect as closely as possible the physiological pH of the skin without compromising the chemical stability of the oxygen-labile species. For example, the preferred pH environment for ascorbic acid should about 5.5 and above. The preferred pH for retinol should be about 5.5 and above. Preferably, the pH should be between about 5.5 and about 9. pH greater than about 10 may result in irritation to the skin when applied topically.

During manufacture of the compositions of this invention, oxygen exposure should be minimized as much as possible so as to reduce the possibility of oxidizing the oxygen-labile species and preserve its stability. Therefore, to the extent possible, all oxygen in the manufacturing system should be displaced with nitrogen or argon gas, as set forth, for example, in U.S. Patent No. 5,559,149.

The compositions of this invention may be used in therapeutic situations wherever the oxygen-labile ingredients are therapeutically active. For example, ascorbic acid can be used for collagen synthesis, elastin synthesis or skin depigmentation and other known uses. Tocopherol, for example, may be useful in free radical scavenging internally or topically. The compositions of this invention may be applied topically to the skin on a daily or more or less frequent basis. The compositions of this invention deliver therapeutic quantities of oxygen-labile species to the skin.

Other emollients and surface active agents have been incorporated in the emulsions, including glycerol trioleate, acetylated sucrose distearate, sorbitan trioleate, polyoxyethylene (1) monostearate, glycerol monooleate, sucrose distearate, polyethylene glycol (50) monostearate, octylphenoxypoly (ethyleneoxy) ethanol,

decaglycerin penta-isostearate, sorbitan sesquioleate, hydroxylated lanolin, lanolin, triglyceryl diisostearate, polyoxyethylene (2) oleyl ether, calcium stearoyl-2-lactylate, methyl glucoside sesquistearate, sorbitan monopalmitate, methoxy polyethylene glycol-22/dodecyl glycol copolymer (Elfacos E200), polyethylene glycol-45/dodecyl glycol copolymer (Elfacos ST9), polyethylene glycol 400 distearate, and lanolin derived sterol extracts, glycol stearate and glycerol stearate; alcohols, such as cetyl alcohol and lanolin alcohol; myristates, such as isopropyl myristate; cetyl palmitate; cholesterol; stearic acid; propylene glycol; glycerine, sorbitol and the like.

The composition of this invention can contain additives, as required, such as a humectant, an antioxidant, a preservative, a flavor, fragrances, a surface active agent, a binder, and the like, as well as skin protectant agents, therapeutic agents and "cosmeceuticals".

Examples of the preservatives include salicylic acid, chlorhexidine hydrochloride, phenoxyethanol, sodium benzoate, methyl para-hydroxybenzoate, ethyl para-hydroxybenzoate, propyl para-hydroxybenzoate, butyl para-hydroxybenzoate and the like.

Examples of the flavor and fragrance include menthol, anethole, carvone, eugenol, limonene, ocimene, n-decylalcohol, citronellol, a-terpineol, methyl salicylate, methyl acetate, citronellyl acetate, cineole, linalool, ethyl linalool, vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, cinnamon leaf oil, perilla oil, wintergreen oil, clove oil, eucalyptus oil and the like.

Examples of surface active agents include sodium alkyl sulfates, e.g., sodium lauryl sulfate and sodium myristyl sulfate, sodium N-acyl sarcosinates, e.g., sodium N-lauroyl sarcosinate and sodium N-myristoyl sarcosinate, sodium dodecylbenzenesulfonate, sodium hydrogenated coconut fatty acid monoglyceride sulfate, sodium lauryl sulfoacetate and N-acyl glutamates, e.g., N-palmitoyl

glutamate, N-methylacyltaurin sodium salt, N-methylacylalanine sodium salt, sodium a-olefin sulfonate and sodium dioctylsulfosuccinate; N-alkylaminoglycerols, e.g., N-lauryldiaminoethylglycerol and N-myristyldiaminoethylglycerol, N-alkyl-N-carboxymethylammonium betaine and sodium 2-alkyl-1-hydroxyethylimidazoline betaine; polyoxyethylenealkyl ether, polyoxyethylenealkylaryl ether, polyoxyethylenelanolin alcohol, polyoxyethyleneglyceryl monoaliphatic acid ester, polyoxyethylenesorbitol aliphatic acid ester, polyoxyethylene aliphatic acid ester, higher aliphatic acid glycerol ester, sorbitan aliphatic acid ester, Pluronic type surface active agent, and polyoxyethylenesorbitan aliphatic acid esters such as polyoxyethylenesorbitan monooleate and polyoxyethylenesorbitan monolaurate. Emulsifier-type surfactants known to those of skill in the art should be used in the compositions of this invention.

Examples of the binder or thickener include cellulose derivatives such as alkali metal salts of carboxymethylcellulose, methyl cellulose, hydroxyethyl cellulose and sodium carboxymethylhydroxyethyl cellulose, alkali metal alginates such as sodium alginate, propylene glycol alginate, gums such as carrageenan, xanthan gum, tragacanth gum, caraya gum and gum arabic, and synthetic binders such as polyvinyl alcohol, polysodium acrylate and polyvinyl pyrrolidone.

Thickeners such as natural gums and synthetic polymers, as well as preservatives such as methylparaben, butyl paraben, propylparaben and phenoxyethanol, coloring agents and fragrances also are commonly included in such compositions.

Other active ingredients such as sunscreen materials and antimicrobial materials may be utilized in the compositions of the present invention provided that they are physically and chemically compatible with the other components of the compositions. For example, moisturizing agents such as propylene glycol, allantoin, acetamine MEA, oat protein and hyaluronic acid and other humectants may be added to the retinoid-containing formulations of this invention in order to provide

moisturizing activity in conjunction with the retinoid-related activity of the products. Other proteins and amino acids may also be incorporated. Sunscreens may include organic or inorganic sunscreens, such as octylmethoxycinnamate and other cinnamate compounds, titanium dioxide and zinc oxide and the like.

Other ingredients may include agents which assist in protecting the skin from aging, such as sunscreens, anti-oxidant vitamins such as ascorbic acid, vitamin B, biotin, pantothenic acid, vitamin D, vitamin E and vitamin C. Yeast extract, gingko biloba, bisabolol, panthenol, alpha hydroxy acids and oligosaccharides such as melibiose are among other ingredients which assist in preventing aging of the skin by such means as irritation mitigation, oxidation mitigation, healing, affecting retinoid metabolism and inhibiting the production of elastase.

Skin color evening ingredients and depigmentation agents may also be effective in the products of this invention. Such ingredients may include hydroquinone, licorice extract, kojic acid, gatuline A (pilewort extract), micromerol (butylene glycol and apple extract), glutathione, arbutin, placenta extract, ascorbic acid, magnesium-L-ascorbyl-2-phosphate and the like.

Compositions which assist in the reduction of lines and wrinkles may also be added to the compositions of this invention. For example, alpha hydroxy acids, hyaluronic acid, Gatuline R (fagus silvitica extract), pigments and scattering aids such as mica, zinc oxide and titanium dioxide may be used in the compositions of this invention in this capacity. Various natural extracts such as tannins, flavenoids, saponins and the like may also be added.

Anti-inflammatory agents may also be used in the compositions of this invention. Not only should these agents assist in mitigating irritation, they may assist the retinoids in treating wrinkles and lines in the skin. Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate,

desonide, desoxycorticosterone acetate, dexamethasone, dichlorisone, deflorasonediacetate, diflucortolone valerate, fluadronolone, fluclarolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocionide, flucortine butylester, fluocortolone, flupredidene (flupredylidene) acetate, flurandronolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, amciafel, amcinafide, betamethasone and its esters, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone and mixtures thereof may be used. Preferably, hydrocortisone may be used.

Nonsteroidal anti-inflammatory agents may also be employed in the compositions of this invention, such as salicylates (including alkyl and aryl esters of salicylic acid), acetic acid derivatives (including arylacetic acid and its derivatives), fenamates, propionic acid derivatives and pyrazoles or mixtures thereof. Other synthetic and natural anti-inflammatory agents may also be used.

Additional active ingredients having topical activity may be utilized in the compositions of this invention. Azole-type anti-fungal and anti-bacterial agents may be employed in the compositions of this invention in their base form. For example, ketoconazole, miconazole, itraconazole, metronidazole, elubiol, and like related imidazole antifungals and antibacterials are useful in the topical formulations of this invention.

The advantages of the invention and specific embodiments of the skin care compositions prepared in accordance with the present invention are illustrated by the following examples. It will be understood, however, that the invention is not

confined to the specific limitations set forth in the individual examples, but rather to the scope of the appended claims.

Example 1: An Emulsion containing A Hydrophilic Oxygen-Labile Species (Ascorbic Acid)

A composition in accordance with this invention was made by combining the following ingredients in a water phase:

Ingredients	% w/w
Water	q.s. to 100%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methylparaben	0.20%
Propylparaben	0.07%
Hydroxyethyl cellulose	0.3%
Xanthan Gum	0.50%

A batch of 1 kilogram was made according to the following process. The weight of the beaker was recorded, and the water then added. Because this process requires boiling, an additional 50 grams of water was added to the beaker to counter the effect of evaporation. The beaker was covered with aluminum foil and beginning boiling the water. The water was permitted to boil for at least five minutes. The heat was turned off, and the water cooled to 80°C. The water phase was kept heated at least for ten minutes. The disodium EDTA was added and the water phase mixed until the EDTA was fully dissolved and clear. The xanthan gum and hydroxyethyl cellulose were slurried into the glycerin in a side container. The slurry was poured into the water phase. Tthe preservatives were added (i.e., the phenoxyethanol, methyl paraben and propyl paraben). The water phase was held at 80°.

Separately, in another container, an oil phase was created using the following ingredients:

Ingredients	% w/w
Butyl hyroxytoluene	0.10%
Glyceryl monostearate & Peg-100 stearate	5.00%
Cetyl palmitate	1.00%
Cetyl alcohol	1.00%
C12-15 alkyl benzoate	4.00%
White petrolatum	1.50%
Butyl Methoxydibenzoyl methane	1.00%
Octyl methoxycinnamate	7.50%

Aall of the above named oil phase ingredients were combined in a beaker, and heated to 80°C. The oil phase was mixed homogeneously. When both phases were at 80°C, the oil was phased into the water phase. The batch was cooled to room temperature. When at 45°C, the post-additions were added to the batch.

Ingredients	%w/w
Ascorbic acid	5.00%
N-acetyl cysteine	0.10%
Ethanol	2.78%
NaOH (20%)	q.s. to desired pH.

The stabilizing compound, in this case the N-acetyl cysteine was added first, and allowed to mix for at least ten minutes. After the requisite mixing, the ascorbic acid was added. The sodium hydroxide was then added to neutralize the batch. The mixer speed was slowed down when the neutralization solution was added to minimize any whipping of air into the beaker. Finally, the ethanol was added , and water added to the batch q.s. The product was filled in aluminum tubes. The compositions may also be placed in any other suitable oxygen impermeable package.

Example 2:

Another composition according to this invention was made including both 2% Vitamin C and 0.1% N-acetyl cysteine. The composition included the following ingredients and was made in accordance with the method set forth in Example 1:

Chemical Name	% wt/wt
Water Phase	
Water	60.72%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylated hydroxytoluene	0.10%
Octyl methoxycinnamate	7.50%
Butyl methoxydibenzoylmethane	1.00%
Glyceryl Stearate (and) PEG-100 Stearate	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12-15} Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Post - additions	
Ascorbic acid	5.00%
n-acetyl cysteine	0.10%
Ethanol	2.78%
NaOH (40%)	2.90%

Another formulation may also be made in accordance with this Example 2, however the 0.1% N-acetyl-cysteine may be replaced with 1% lactoferrin or iniferrin.

Example 3:

The following is another formulation that may be made in accordance with this invention, containing ubiquinone, an anti-oxidant. The following formulation may be made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
Water Phase	
Water	64.62%
Disodium EDTA	0.10%
Dex Panthenol	1.00%
Preservatives	0.73%
carbomer	0.35%
Oil Phase	
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Caprylic/Capric Triglycerides	3.00%
Cetyl Alcohol	2.00%
Octyl hydroxystearate	2.00%
C_{12-15} Alkyl Benzoate	4.00%
Butyl methoxydibenzoylmethane	3.00%
Octyl methoxycinnamate	7.50%
Post - Additions	
Ubiquinone	0.10%
Lactoferrin (and) Thioxanthine (and) Uric Acid	0.50%
Cyclomethicone	1.50%
NaOH (10%)	4.60%
	100.00%

** adjust NaOH concentration to desired pH.

This formulation should be stable over a period of time and under exposure to heat.

Example 4:

The following is another formulation that may be made in accordance with this invention, containing ascorbyl palmitate, an anti-oxidant. The following formulation may be made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
Water Phase	
Water	64.62%
Disodium EDTA	0.10%
Glycerin	3.50%
Xanthan Gum	0.50%

Magnesium Aluminum Silicate	1.00%
Preservatives	1.00%
Oil Phase	
Cetearyl Glucoside	3.00%
Stearyl Alcohol	1.50%
Cetyl Alcohol	1.50%
Octyl hydroxystearate	2.00%
C_{12-15} Alkyl Benzoate	4.00%
Dimethicone	1.00%
Ascorbyl Palmitate	0.50%
Octyl methoxycinnamate	4.00%
Post - additions	
N-acetyl cysteine	0.01%
Green Tea Extract	
Chamomile Extract	
NaOH (10%)	4.60%

Example 5:

The following is another formulation that may be made in accordance with this invention, containing hydroquinone, a skin-bleaching agent. The following formulation may be made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
Water Phase	
Water	75.32%
Propylene Glycol	2.00%
Dex Panthenol	1.00%
Preservatives	0.73%
carbomer	0.35%
Oil Phase	
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Mineral Oil	4.00%
Stearic Acid	2.00%
Petrolatum	1.00%
Post - Additions	
Hydroquinone	2.00%
Lactoferrin (and) Thioxanthine (and) Uric Acid	2.00%
NaOH (10%)	4.60%
	100.00%

** adjust NaOH concentration to desired pH.

Example 6:

The stability of different formulations containing retinol, ascorbic acid and/or tocopherol as set forth in Examples 7 and 8 below were monitored in terms of appearance and HPLC assay. The degraded products of retinol, ascorbic acid or tocopherol are yellow or brownish in color. The freshly prepared samples were white creams. Discoloration to yellow or brown indicates the instability.

Effect of 1% Iniferine on Retinol, Ascorbic acid and Tocopherol stability (no BHT, no EDTA)

Example #	Active	Assay (4°C, 4 weeks)	Color (4°C, 4 weeks)	Assay (40°C, 4 weeks)	Color (40°C, 4 weeks)
Example 7	Retinol	0.168	White (no discoloration)	0.122 (72.6%)	Yellowish (discolored)
	Ascorbic acid	4.8		4.68 (97.5%)	
	Tocopherol	0.95		0.64 (67.4%)	
Example 8	Retinol	0.174	White (no discoloration)	0.165 (94.8%)	White (no discoloration)
	Ascorbic acid	4.81		4.63 (96.5%)	
	Tocopherol	1.01		0.98 (97.0%)	

If ascorbic acid is removed from the formulations, as set forth below, the formulations are not as stable, even with additional BHT and EDTA. However, formulations containing ascorbic acid and tocopherol were found to be stable. Thus, ascorbic acid assists in stabilizing tocopherol.

Effect of 5% Ascorbic acid on Retinol and Tocopherol stability

Example #	active	Target value	25°C, 1 week	Color
Example 9	Retinol	0.1725	0.1695	White (no discoloration)
	Ascorbic Acid	5.00	4.96	
	Tocopherol	1.00	0.96	
Example 10	Retinol	0.1725	0.15	Bright yellow (discolored
	Tocopherol	1.00	0.89	

Due to the immediate loss of retinol and tocopherol and significant discoloration, no further stability was conducted on Example 10. The addition of N-acetylcysteine slightly enhances the stability of retinol and tocopherol.

Effect of Ascorbic concentration on Ascorbic acid, Retinol and Tocopherol Stability (compositions referred to in Example 9)

Initial Ascorbic concentration	active	8 weeks @ 4°C	8 weeks @ 40°C
0.1%	Retinol	0.1655 (100%)	0.1600 (96.7%)
	Ascorbic Acid	0.05 (100%)	0.04 (80%)
	Tocopherol	0.98 (100%)	1.00 (100%)
1%	Retinol	0.1582 (100%)	0.1603 (100%)
	Ascorbic Acid	0.89 (100%)	0.80 (89.9%)
	Tocopherol	0.99 (100%)	0.99 (100%)
10%	Retinol	0.1657 (100%)	0.1664 (100%)
	Ascorbic acid	9.80 (100%)	9.90 (100%)
	Tocopherol	1.10 (100%)	1.12 (100%)

If we refer to the stability of the compositions at 8 weeks at 40°C as the initial, all A (retinol), C (ascorbic acid), E (tocopherol) samples are stable. The data also suggests that it is important to control the manufacturing process for low concentration ascorbic acid to minimize any loss in stability.

Example 7:

A formulation according to this invention was made containing Vitamins A, C, E and iniferine. It did not include BHT, an antioxidant or disodium EDTA, a chelating agent.

Chemical Name	% wt/wt
Water Phase	
Water	65.15%
Disodium EDTA	0.00%
Glycerin	5.00%
Preservative	0.73%
Preservative	0.35%
Preservative	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.00%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12}-C_{15} Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Post - Additions	

Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	0.00%
Ethanol	2.78%
NaOH (20%)	5.62%

Example 8:

A formulation according to this invention was made containing Vitamins A, C, E and iniferine. It included BHT, an antioxidant and disodium EDTA, a chelating agent.

Chemical Name	% wt/wt
Water Phase	
Water	64.15%
Disodium EDTA	0.00%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.00%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12}-C_{15} Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Post - Additions	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

Example 9:

Another formulation according to this invention was made containing Vitamins A, C and E but did not include sunscreens. The composition was made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
Water Phase	
Water	63.95%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.10%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12}-C_{15} Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Post - Additions	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

Another 3 formulations containing 0.1%, 1% and 10% ascorbic acid respectively were made in accordance with example 9, however, 1% lactoferin/thioxanthine/uric acid was replaced with 1% lactoferrin.

Example 10:

Yet another formulation was made in accordance with the method set forth in Example 1. This composition contained Vitamins A and E and iniferine.

Chemical Name	% wt/wt
Water	68.95%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%

Xanthan Gum	0.50%
Butylhydroxytoluene	0.10%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12-C15} Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

Example 11:

A formulation containing

Chemical Name	% wt/wt
Water Phase	
Water	52.85%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.10%
Octyl methoxycinnamate	
Avobenzone	3.00%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C_{12-C15} Alkyl Benzoate	
White Petrolatum	1.50%
Post - Additions	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Polysorbate 20	1.00%
Lactoferrin, thioxanthine, uric acid	1.00%

Ethanol	2.78%
NaOH (20%)	5.62%

Example 12:

A composition was made in accordance with this invention containing Vitamins A and C with Iniferine alone without N-acetyl cysteine. After 13 weeks exposure to 40°C, 95% of the Vitamin C was retained and there was no loss in A.

Chemical Name	% wt/wt
Water Phase	
Water	73.96%
Disodium EDTA	0.20%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	1.00%
Oil Phase	
Butylhydroxytoluene	0.10%
GMS	2.00%
Cetearyl Glucoside	3.00%
C12-15 alkyl benzoate	2.00%
Avobenzone	2.00%
Octyl methoxycinnamate	4.00%
Ascorbyl Palmitate	0.50%
Post - Additions	
ascorbic acid	2.00%
n-acetyl cysteine	0.00%
Retinol 50c	0.27%
uric acid	1.00%
isoparaffin; laureth-7; polyacrylamide	1.50%
NaOH	5.47%

Example 13:

The following composition contained only Vitamin C with N-acetyl cysteine. It was made in accordance with the procedure set forth in Example 1 except that the composition was boiled rather than purged with inert gas to remove oxygen.

Chemical Name	% wt/wt
Water Phase	
Water	64.92%
Disodium EDTA	0.10%

Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.10%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C12-C15 Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Avobenzone	1.00%
Octyl methoxycinnamate	7.50%
Post - Additions	
Ascorbic Acid	2.00%
ethanol	2.78%
n-Acetyl Cysteine	0.10%
NaOH (10%)	1.70%

After exposure to 50°C for 13 weeks, 96% of the Vitamin C remained in this composition.

Example 14:

A composition in accordance with this invention was made using the procedure set forth in Example 1. This composition contained Vitamins A and C as well as Iniferine and N-acetyl cysteine. After 13 weeks incubation at 40°C, 90% C and 96% A remained in the composition.

Chemical Name	% wt/wt
Water Phase	
Water	51.27%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.15%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.10%

Octyl methoxycinnamate	7.50%
Avobenzone	3.00%
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C12-C15 Alkyl Benzoates	4.00%
White Petrolatum	1.50%
Post - Additions	
Ascorbic Acid	5.00%
Tocopherol	0.05%
Retinol	0.25%
Lactoferrin; thioxanthine; uric acid	1.00%
n-acetyl cysteine	0.01%
Ethanol	2.78%
NaOH (20%)	9.04%

Example 15:

A composition in accordance with this invention was made using the procedure set forth in Example 1. This composition contained Vitamins A, C and E as well as Iniferine and N-acetyl cysteine. After 11.5 weeks incubation at 40°C, 92% of the Vitamin A, 99% of the Vitamin C and 97% of the Vitamin E remained in the composition.

Chemical Name	% wt/wt
Water Phase	
Water	53.45%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Oil Phase	
Butylhydroxytoluene	0.10%
Octyl methoxycinnamate	7.50%
Avobenzone	3.00%
Glyceryl Monostearate & PEG-100	5.00%
Octyl Hydroxstearate	2.00%
Cetyl Alcohol	2.00%
C12-C15 Alkyl Benzoate	5.00%
Post - Additions	
Ascorbic Acid	2.00%

Tocopherol	1.00%
Retinol	0.25%
Lactoferrin; thioxanthine; uric acid	1.00%
n-acetyl cysteine	0.01%
Cyclomethicone	1.50%
NaOH (10%)	

Of course, the foregoing examples are merely illustrative of the compositions and methods of this invention and do not represent its full scope.

WHAT IS CLAIMED IS:

1. Compositions containing oil-soluble and/or water-soluble oxygen-labile species comprising oil-soluble or water-soluble oxygen-labile species and one or more stabilizer compounds selected from the group consisting of:

a) thio-containing compounds; and

b) glycoproteins.

2. Compositions according to claim 1 wherein said thio-containing compounds are selected from the group consisting of sulfites, metabisulfites, glutathione and cysteine derivatives.

3. Compositions according to claim 1 wherein said glycoprotein is lactoferrin.

4. Compositions according to claim 3 wherein said composition further comprises thioxanthine and uric acid.

5. Compositions according to claim 1 wherein said oil-soluble oxygen-labile species are selected from one or more of the group consisting of retinoids, choleciferol, vitamin K tocotrienol, fatty acids, and tocopherol and their derivatives.

6. Compositions according to claim 1 wherein said water-soluble oxygen-labile species are selected from one or more of the group consisting of ascorbic acid and its derviatives, niacin, thiamine, riboflavin, folic acid, pyrodoxine, pantothenic acid, niacinamide, lipoic acid, dihydrolipoic acid, amino acids and their derivatives.

7. A composition according to claim 2 wherein said thio-containing compound is N-acetylcysteine.

8. Compositions according to claim 1 wherein said composition comprises one or more retinoids and one or more tocopherols and one or more ascorbic acid or its derivatives.

9. Compositions according to claim 1 wherein said composition comprises ascorbic acid and tocopherol or their derivatives.

10. Compositions according to claim 1 wherein said composition comprises retinoids and ascorbic acid or its derivatives.

11. Compositions according to claim 1 wherein said composition comprises retinoids.

12. Compositions according to claim 1 wherein said composition comprises ascorbic acid or its derivatives.

13. Compositions according to claim 1 wherein said composition comprises tocopherol or its derivatives.

14. Compositions according to claim 8 wherein said compositions comprise lactoferrin or iniferine.

15. Compositions according to claim 8 wherein said compositions comprise N-acetyl cysteine.

16. A method of stabilizing compositions containing oil-soluble or water-soluble oxygen-labile species or combinations thereof comprising adding to said compositions oil-soluble or water-soluble oxygen-labile species one or more stabilizer compounds selected from the group consisting of:

a) thio-containing compounds; and

b) glycoproteins.

ABSTRACT

This invention relates to compositions and methods for stabilizing oxygen-labile species. More particularly, it relates to compositions containing one or more oil- and/or water-soluble oxygen-labile species and one or more stabilizing elements. It also relates to methods of making such compositions and methods of using such compositions.

DOCKET NO. JBP 461

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled COMPOSITIONS FOR STABILIZING OXYGEN-LABILE SPECIES, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

60/136,442 (Application Number) — May 28, 1999 (Filing Date)

_____ (Application Number) — _____ (Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Andrea L. Colby (Reg. #30,194), Michael Stark (Reg. #32,495), and William E. McGowan (Reg. #39,301), One Johnson & Johnson Plaza, New Brunswick, NJ 08933.

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